

Claims

1. A process for the isolation and purification of HMG-CoA
5 reductase inhibitors from a mycelium biomass which comprises:
- clarifying a mycelium broth and concentrating the clarified
broth to a lower volume,
- acidifying of the concentrate to a pH value in the range of
4.5 to 7.5, followed by extracting the HMG-CoA reductase
10 inhibitor with ethyl acetate,
- optionally performing lactonization,
- crystallization of the HMG-CoA reductase inhibitor from a
water-miscible or water-soluble organic solvent, and
- crystallization of the HMG-CoA reductase inhibitor from an
15 organic solvent having limited miscibility or solubility
with water.
2. The process according to claim 1, further comprising,
before clarifying the mycelium biomass broth, the steps of
20 dissolving the HMG-CoA reductase inhibitor from a mycelium
biomass at pH value between 9.5 and 13 into fermentation
liquor, and adjusting the broth to a pH value between 7.5 and
8.5.
- 25 3. The process according to claim 2, wherein the dissolution
step is carried out at a temperature in the range of 10 to 40°C
for less than one hour.
- 30 4. The process according to any one of the preceding claims,
wherein clarifying the mycelium broth is carried out by
removing the mycelium from the broth by means of filtration.
- 35 5. The process according to any one of the preceding claims,
wherein said clarified broth is concentrated by means of
reverse osmosis.

6. The process according to any one of the preceding claims, wherein the concentrate is acidified to a pH value in the range of 5.5 to 7.5.

5 7. The process according to claim 6, wherein the concentrate is acidified to a pH value in the range of 6.0 to 7.0.

8. The process according to any one of the preceding claims, wherein the HMG-CoA reductase inhibitor which is extracted
10 from ethyl acetate and optionally lactonized is subjected to a purification step by adsorption chromatography.

9. The process according to claim 8, wherein a mixture of acetonitrile and water is used as the mobile phase for
15 adsorption chromatography.

10. The process according to any one of the preceding claims, wherein the order of the crystallization steps is reversed.

20 11. The process according to any one of the preceding claims, wherein the water-miscible or water-soluble organic solvent used in the crystallization step is acetone or a low alkyl alcohol.

25 12. The process according to claim 11, wherein the crystallization step comprises dissolving the HMG-CoA reductase inhibitor in acetone, and then adding water thereto.

30 13. The process according to any one of the preceding claims, wherein the crystallization step from an organic solvent having limited miscibility or solubility with water comprises dissolving the HMG-CoA reductase inhibitor in said organic solvent at a concentration of 10 to 35 g/l, and removing one-third to three-fourth of said organic solvent.

35 14. The process according to any one of the preceding claims, wherein the organic solvent having limited miscibility or

00500566-101500

January 24, 2000

PCT Patent Application PCT/IB99/00808
LEK PHARMACEUTICAL AND CHEMICAL CO., D.B. et al.
Our ref.: WO 21555

- 17 -

solubility with water used in the crystallization step is ethyl acetate.

15. The process according to any one of the preceding claims,
5 wherein HMG-CoA reductase inhibitors are obtained having a
purity higher than 99.6%.

16. The process according to any one of the preceding claims,
wherein the HMG-CoA reductase inhibitor is selected to be
10 lovastatin.

17. A process for the purification of HMG-CoA reductase
inhibitors which comprises subjecting the HMG-CoA
reductase inhibitor to combined crystallization steps, which
15 comprises crystallization from an water-miscible or water-
soluble and crystallization from an organic solvent having
limited miscibility or solubility with water, as final
polishing steps to obtain HMG-CoA reductase inhibitors having a
purity higher than 99.6%.

18. The process according to claim 17, wherein the obtained
HMG-CoA reductase inhibitors have purity higher than 99.7 %.

19. The process according to claim 1 or 18, wherein wherein
25 acetone or a low alkyl alcohol is used as the water-miscible or
water-soluble organic solvent.

20. The process according to claim 19, wherein said
crystallization comprises dissolving the HMG-CoA reductase
30 inhibitor in acetone, and then adding water thereto.

21. The process according to any one of claims 17 to 20,
wherein said crystallization from said organic solvent having
limited miscibility or solubility with water comprises
35 dissolving the HMG-CoA reductase inhibitor in said organic
solvent at a concentration of 10 to 35 g/l, and removing one-
third to three-fourth of said organic solvent.

24¹⁸0100

22. The process according to any one of claims 17 to 21, wherein ethyl acetate is used as the organic solvent having limited miscibility or solubility with water.

5

23. Use of a process according to claim 1 or a process according to claim 17 for the isolation and/or purification of lovastatin.

add
a'

Add

E7

00500556-101600